REMARKS/ARGUMENTS

The Office Action dated August 26, 2003, has been carefully considered. The Applicants respectfully request reconsideration of the application in view of the following arguments and remarks.

Double Patenting

The provisional nonstatutory double patenting rejection has been noted. The Applicants respectfully request that this provisional rejection be held in abeyance until allowable subject matter in the present application is indicated.

Claims 39-75 stand rejected under 35 USC 112, first paragraph, for lack of enablement, for the indicated reasons.

In Paragraphs 4 and 5 of the Official Action, the Examiner has rejected all pending claims on the basis that the Applicants' specification does not enable a person skilled in the art how to choose a compound other than those disclosed in the claims of the parent U.S. Patent No. 6,350,760, for use as a selective melanocortin-4 receptor (MC-4R) agonist for the treatment of male erectile dysfunction (MED). The Examiner maintains that the Applicants' specification does not enable the ordinary artisan how to make and/or how to use the invention without "extensive and undue experimentation." The Applicants respectfully disagree since they believe that their specification does provide sufficient direction and guidance to enable the skilled artisan how to discover MC-4R agonists as well as how to use them to treat MED without undue experimentation.

The invention of Claims 39-75 is a method of treating MED with a compound that is a selective agonist of MC-4R as defined by the scope of the claims. The critical inventive parameter is selective activation of MC-4R. The present application clearly sets out for the skilled artisan how to identify compounds which **bind selectively** to MC-4R and which also function as **agonists** of MC-4R according to the parameters of Claims 39-75 and then proceeds to describe how to evaluate their therapeutic properties in several *in vivo* models of MED. The methods to be used to identify selective binders of MC-4R are given on page 35 of the specification which details the assays that measure binding affinities to five different melanocortin receptor subtypes. Next the methods needed to determine whether the

selective binders of MC-4R also function as selective agonists of MC-4R are provided by a description of the functional assays on page 37 of the specification. These functional assays discriminate MC-4R agonists from antagonists. By a selective MC-4R agonist is meant a compound that binds to MC-4R and initiates a pharmacological response characteristic of only that receptor, that is, a compound that activates MC-4R and not the other four MC-R's. Finally, methods to use MC-4R-selective agonists to treat MED are provided on pages 38-39 of the specification which describe the rat *ex copula* model. Thus, how to identify and how to use compounds within the scope of Claims 39-75 are clearly set out in Applicants' specification. The identity of such compounds is not limited to, but is merely exemplified by, the 4-substituted piperidines of Formula (I) of the instant application. Since the Applicants' specification enables the "critical or essential method parameters which are necessary to the practice of the invention," no undue experimentation is required other than carrying out what is taught in the specification. Example 84 constitutes a working example which clearly illustrates the operability of the present invention. The compound disclosed in Example 84 is representative of compounds that are selective agonists of human MC-4R within the scope of the claims which induce penile erections in the rat when administered either by the oral or parenteral route. The Applicants are willing to provide extrinsic evidence in the form of additional compounds which have been identified using the teachings found in the specification of the instant application.

Once a compound having the receptor binding and functional properties within the parameters of Claims 39-75 is identified, then the preparation of a pharmaceutical composition for systemic administration, as well as determining an appropriate dose and the route of administration, can be accomplished following the methods described in the instant application or modifications thereof which are known to one of ordinary skill in the pharmaceutical arts. Although some experimentation may be necessary, the pharmaceutical arts typically engage in such activity in the drug discovery process. The test of enablement is not whether any experimentation is necessary, but whether such necessary experimentation is undue (quoting from MPEP 2164.01). Moreover, the applicant need not demonstrate that the invention is completely safe (quoting from MPEP 2164.01(c)). Thus, the Applicants submit that one reasonably skilled in the art could make/use the present invention from the disclosures in the instant application coupled with information known in the art without undue experimentation.

Therefore, the Applicants submit that Claims 38-75 are fully enabled by their specification, and they therefore respectfully request that this section 112, first paragraph, rejection be withdrawn.

Claims 39-75 stand rejected under 35 USC 112, first paragraph, for lack of written description.

The Examiner stipulates that the Applicants' specification does not provide any guidance with respect to how to choose a compound outside the scope of the instant Formula (I) that would fulfill the requirements of the claims, that is, that there is no "description" of the identifying characteristics for recognizing that a compound is a candidate for the claims. The Applicants respectfully disagree with the Examiner's contention. Although the Applicants describe compounds of Formula (I) as being selective MC-4R agonists, such compounds are merely representative of other structural types that may also be selective agonists. A relationship had been established in the art between the **function** of binding to the family of G-protein-coupled receptors to which MC-4R belongs and the **structure** of potential ligands having affinity for such receptors. A review of these so-called "privileged structure" based ligands of G-protein-coupled receptors has published in Annual Reports in Medicinal Chemistry, Vol. 35, pp 289-298 (2000) (a copy of which is enclosed for reference by the Examiner) and is exemplified by the discovery of chemokine CCR5 antagonists described in Expert Opin. Ther. Patents, 13: 1469-1473 (2003). Thus, privileged structures and their affinity for G-protein coupled receptors were well appreciated in the medicinal chemical arts at the time of filing of Applicants' patent application. Indeed it was Applicants' recognition of this art that led them in the first place to focus on 4-substituted piperidines of Formula (I) as potential selective ligands for MC-4R. However, 4-substituted piperidines are merely one class of such privileged structure scaffolds known in the G-protein-linked receptor art. Other structurally diverse variants outside the scope of Formula (I) make up a rich pool of compounds from the G-protein-linked receptor art for evaluation according to the methods described in the instant application. They include *inter alia* compounds having a 1,1-diphenylmethyl, benzodiazepine, biphenyl, tricyclic aromatic, 4-arylpiperidine and spiro versions thereof (such as spiroindanylpiperidine), 4-arylpiperazine, peptidyl, and peptidomimetic structural motif. Thus, guidance for the selection of compounds beyond those of Formula (I) that would fulfill the requirements of the instant claims was and continues to be provided by the art. Hence, there does exist in the art definite structural

characteristics for recognizing candidate compounds with the potential to function as selective MC-4R agonists thereby providing clear guidance with respect to how to choose a compound outside the scope of Formula (I).

Therefore, the Applicants submit that their specification contains an adequate written description of their invention, and they therefore respectfully request that this section 112, first paragraph, rejection be withdrawn.

The Applicants believe that all of the objections and rejections have been overcome by argument, and therefore earnestly solicit an early allowance of the claims remaining under consideration.

Respectfully submitted,

By _____

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Enclosure